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Data Available on the Extent of Cocaine Use and Dependence: Biochemistry, Pharmacologic Effects and Global Burden of Disease of Cocaine Abusers

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Abstract: Drug use is seen more as an individualistic behaviour and is therefore not readily conceived of from a population perspective. There is general recognition of several phases and degrees of drug abuse, from initiation and early-use patterns to long-term chronic use. Cocaine and its derivative "crack" cocaine provide an example of both the globalization of substance use and the cyclical nature of drug epidemics. Cocaine is a powerful CNS (Central Nervous System) stimulant but exerts its action in a several types of adverse health effects, including acute toxic effects (i.e. overdose, accidental injury and violence), dependence, cardiovascular disease, cirrhosis, blood-borne bacterial and viral infections, and mental disorders. Of interest, many people who use Cocaine will use also other drugs; therefore, ascribing adverse health effect to a certain drug might be difficult. Any mucous membrane can act as a port of entry for cocaine and the systemic effect is greatly influenced by the route and speed of administration. The effects of Cocaine mainly depend on the user's addiction, the dose received and the mode of assumption. Laws restricting the availability of cocaine saw a decrease in consumption in these countries until the 1960s. The number of cocaine users worldwide ranged from 14 million to 21 million (0·3–0·5% of the population aged 15–64 years). The largest market was North America, then western and central Europe and South America.

Keywords: Cocaine abuse, laws restricting, "crack", epidemiology, dependence, cardiovascular disease.

INTRODUCTION

Drug use is seen more as an individualistic behaviour and is therefore not readily conceived of from a population perspective. One of the most important challenges to drug abuse epidemiologists is defining and measuring the phenomenon of study.

There is general recognition of several phases and degrees of drug abuse, from initiation and early-use patterns to long-term chronic use. Age of onset is an important measure, as many studies have found a relationship between age of onset and subsequent drug abuse or drug dependency (using either the Diagnostic and Statistical Manual or the International Classification of Diseases) [1, 2].

The paper by Glantz and Colliver [3] addresses the need to develop better definitions and measures of drug-using behaviours in order to better understand this phenomenon and improve policies and prevention and treatment approaches to stem the behaviour and its associated social and health problems.

The availability of drugs and the ways in which drugs are marketed also influence which types of drugs are used and who uses them [4]. The type, quality and price of drugs also influence use [5-8]. An understanding of the importance of the social factors that influence drug abuse trends should guide national and local policies regarding approaches to be taken to alter the devastating consequences of the problem [9, 10].

There is extensive literature that implicates a range of risk factors for drug use, including parent-child attachment, parental monitoring, peer association and school failure [11]. Researchers have made an effort to organize these in such a way as to generate hypotheses about the origins of drug use that could be targeted in prevention strategies [12, 13].

Research also shows that the more risk factors a person experiences in their youth, the more likely it is that drug abuse will occur [14].

Recent research into why many adolescents with such risk factors for drug use do not abuse drugs has shown that certain factors temper risks [15]. These tempering or protective factors include family bonding and bonding to prosocial groups, behaviours and institutions [16]. There is also a growing focus on less well-articulated factors, such as resilience and positive assets [17].However, all of these approaches to the issue of onset lack specificity for drug abuse.

COCAINE ABUSE

Cocaine and its derivative "crack" cocaine provide an example of both the globalization of substance use and the cyclical nature of drug epidemics. Traditionally coca leaves have been chewed by people in the Andean countries of South America for thousands of years. The main alkaloid of the coca leave, cocaine, was isolated relatively recently in about 1860. Cocaine was then used in patent medicines, beverages and "tonics" in developed countries in Europe, North America and in Australia until the early 1900s. Laws restricting the availability of cocaine saw a decrease in consumption in these countries until the 1960s. From that time cocaine use became popular among certain groups of young people in some developed countries and in the producer countries of South America. Cocaine became widely available in North America in the 1970s and Europe in the 1980s. Prevalence rates for lifetime use of cocaine are typically 1% - 3% in developed countries, with higher rates in the United States and in the producer countries. "Crack" or smokable cocaine was being used in Peru in the 1970s but came to the United States in 1985 [18]. Crack cocaine appeared in Canada in 1986 and in European countries somewhatlater [19, 20].

Whilst the threat of widespread "crack epidemics" in Europe have, as yet, proved to be unfounded cocaine and crack are available in most European cities. There are few prevalence estimates of cocaine use in European countries, although available evidence suggests some modest increases in use [21].

Cocaine use rapidly gained in popularity in some developing countries outside of the producer countries and in Central and Eastern Europe. In Mexico City use of cocaine among high school students shows a slow but steady increase from 0.9% lifetime prevalence in 1976 to 1.66% in 1993 [22, 23].

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Actually cocaine use could be considered stabilised in the United States, where in the late 1980s and early 1990s the use of cocaine, and in particular, crack cocaine had become a major illicit drug problem.

During the 19th century, cocaine was available in the United States as an ingredient in patent medicines and was prescribed by physicians for a variety of physical and mental ailments. However, cocaine was not regulated until the Harrison Narcotic Act in 1914. Thereafter, all producers and distributors of cocaine were required to maintain records and register with the Federal Government. Cocaine was first defined as a narcotic in 1922, and the importation of cocaine and coca leaves was prohibited except for controlled pharmaceutic purposes (Amendment to Narcotic Drugs and Export Act 1922).

Most illicit drug use increased after 1972, reached its highest level in 1979, and then declined more or less steadily. Illicit cocaine use, in contrast, did not reach its peak until the mid 1980s [24].

The 2011 world drug report by the UN Office on Drugs and Crime (UNODC) estimated that 149–271 million people aged 15–64 years (3·3–6·1%) had used an illicit drug at least once in 2009. The drugs used varied substantially across regions and these numbers are not mutually exclusive, because some people used more than one drug type [25].

CHEMISTRY

Cocaine occurs in abundance in the leaves of the coca shrub (*Erythroxylum coca*) and is an ester of benzoic acid and methylecgonine Fig. (**1**). Ecgonine is an amino alcohol base closely related to tropine, the amino alcohol in atropine. Cocaine possesses pockets with both high hydrophilic and lipophilic efficiency, violating the rule of hydrophilic-lipophilic balance. This causes it to cross the blood-brain barrier with vastly superior reinforcement than to other psychoactive chemicals.

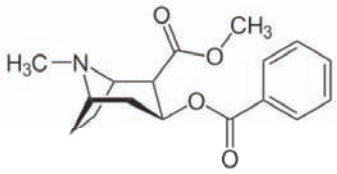

Fig. (1). Chemical structure of Cocaine.

PHARMACOKINETIC PROFILE

Any mucous membrane can act as a port of entry for cocaine and the systemic effect is greatly influenced by the route and speed of administration. It is usually 'snorted', but may be absorbed through the mucous lining of the mouth, rectum or vagina. It can be injected (producing a more intense feeling), but smoking is most common. Crack is Cocaine that has been processed from Cocaine hydrochloride to a free base for smoking. It is rapidly absorbed from the lungs and reaches the cerebral circulation in approximately 6–8 s. When injected, the drug takes approximately twice as long to reach the brain [26]. Snorting cocaine produces euphoria in about 3–5 min [27]. Its vasoconstrictive properties slow its own absorption and achievement of peak plasma concentrations can be delayed for up to 60 min [28]. Cocaine has a relatively short half-life in plasma ranging from 0.5 to 1.5 h, with highest concentrations being found in the brain, spleen, kidney and lung [29].

Cocaine is mainly metabolized by two distinct patways in humans. The major transformation consists of hydrolysis of the ester groups, which is apparently not important in the toxic manifestations [30]. The minor route is an oxidative one involving the amine moiety, which has attracted most attention relative to some toxic responses [31].

Cocaine is primarily (80-90%) metabolized by the 3 esterases pseudocholinesterase, human carboxylesterase-1 (hCE-1), and human carboxylesterase-2 (hCE-2) [32-35].

Fig. (**2**) shows that Cocaine is hydrolyzed mainly by hCE-1 to benzoylecgonine, the primary metabolite excreted in the urine, or by pseudocholinesterase and hCE-2 to ecgonine methyl ester. In the presence of ethanol, hCE-1 catalyzes transesterification of cocaine to cocaethylene, a toxic metabolite, that can be further hydrolyzed by hCE-1 to benzoylecgonine or by hCE-2 to ecgonine ethyl ester [32-34]. The main metabolite benzoylecgonine could be detected in urine for 2 to 3 days after an intranasal dose of 100 mg of cocaine, for 1.5 days after a single intravenous dose of 20 mg, and for 10 days after chronic intravenous doses of 8 g/d [36]. The detection time of Cocaine in blood is 4 to 6 hours after 20 mg and 12 hours after 100 mg. In the serum of chronic users, benzoylecgonine was detectable for 5 days on average [36]. At this point, it must be mentioned that Cocaine may be enzymatically degraded in blood samples during transport and storage, which can be avoided by the use of blood sampling devices containing the cholinesterase inhibitor sodium fluoride [37].

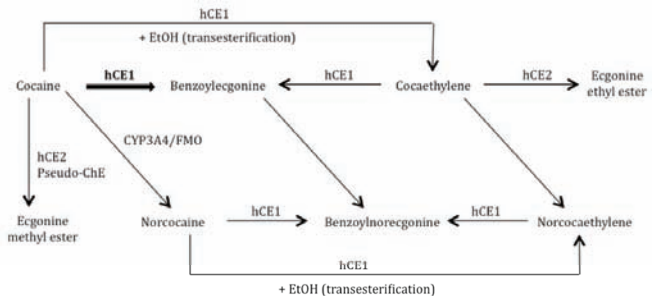

Fig. (2). Major metabolic pathways of Cocaine in humans with the isoenzymes involved.

Concentrations of plasma cholinesterase and hence the half-life of the drug vary [38]. Brock and Brock [39] showed significant effect on individual plasma cholinesterase activity by body weight, height, gender and cholinesterase-1 phenotype (but not by age) among healthy volunteers. Varying body weight explained one-quarter of this observed biological variance. As well as interindividual variations, intraindividual variations in plasma concentration of the enzyme were observed over the 8 month study. Gender differences with cocaine pharmacology exist. Males achieve higher peak plasma cocaine concentrations and experience a greater number of intense good and bad effects from the drug compared with females. Despite these differences in blood concentrations and subjective effects, peak heart rates did not differ between the sexes, suggesting that females may be more sensitive than males to the cardiovascular effects of the drug [40]. This may vary even within the menstrual cycle, with higher peak levels being found during the follicular phase compared with the luteal phase.

As far as the the oxidative metabolism of Cocaine Fig. (**2** and **3**), the first step is N-demethylation to pharmacologically active norcocaine catalyzed by 2 alternate pathways, one involving only CYP3A450 and the other requiring both CYP and flavin-containing monooxygenase. In the first pathway, Cocaine was directly N-demethylated to norcocaine by CYP and the second route was found to be a 2-step reaction involving cocaine N-oxide as an intermediate. In this pathway, cocaine is first oxidized to cocaine N–oxide by flavin-containing monooxygenase, followed by a CYP catalyzed N-demethylation to norcocaine [41]. Again, in the presence of ethanol, hCE-1 catalyzes transesterification of norcocaine to norcocaethylene that can be further hydrolyzed by hCE-1 to benzoylnorecgonine [32-34].

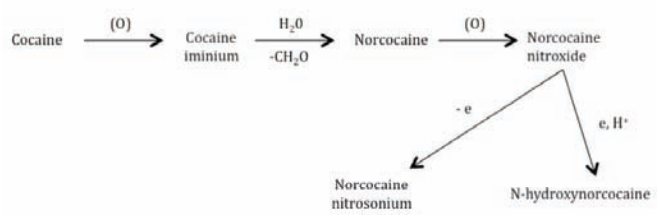

Fig. (3). Oxidative metabolism of Cocaine.

The effects of Cocaine, including its toxicity, may be affected by compounds resulting from its oxidative metabolism, particularly when these compounds are able to cross the blood brain barrier. In this regard, it has been demonstrated that cocaine and norcocaine are neurotoxic [42]. Since cocaine and norcocaine are cationic amphiphiles, it has been suggested that the neurotoxicity induced by Cocaine may require intracellular penetration of Cocaine and trapping in an acidic intracellular compartment [42], since when positively charged it may accumulate in negatively charged compartments, such as mitochondria.

Possible metabolites participating in the effect of Cocaine, in addition to the drug itself, are norcocaine, norcocaine nitroxide, N-hydroxynorcocaine, norcocaine nitrosonium, cocaine iminium and formaldehyde [31].

All these oxidative metabolites play important roles compromising oxidative stress (OS), reactive oxygen species (ROS) and electron transfer. Most attention has been devoted to the nitroxide-hydroxylamine couple which has been designated by various investigators as the principal source of ROS. Toxicity by Cocaine, with evidence for participation of OS, is demonstrated for many body components, including liver, central nervous system, cardiovascular system, reproductive system, kidney, mitochondria, urine, and immune system. Other adverse effects associated with ROS comprise teratogenesis and apoptosis. Examples of ROS generated are lipid peroxides, hydroxyl radical and depletion of glutathione [31].

PHARMACOLOGICAL ACTIONS

Cocaine is a psychomotor stimulant that produces its major pharmacological effects by inhibiting the reuptake of the monoamines dopamine, norepinephrine, and serotonin into presynaptic terminals. Reuptake is the main mechanism by which these neurotransmitters are removed from the extracellular space, and thus from activation of receptors [43]. As a consequence of these actions, Cocaine potentiates neurotransmission of all three monoamines [44-46]. This occurs in both central and peripheral nervous system and the result is increased receptor stimulation (α-adrenoreceptor, β- adrenoreceptor and dopamine) via an indirect sympathomimentic action.

Chronic use of Cocaine produces changes in these neurotransmitter systems as measured by reductions in the neurotrasmitter metabolites MHPG (3-methoxy-4 hydroxyphenethyleneglycol) and 5-HIAA (5-hydroxyindoleacetic acid) [44-46].

The major behavioral effect of Cocaine is that of a psychomotor stimulant, thus it increases locomotor activity when administered to animals [47]. This behavior is believed to be produced primarily by its inhibition of dopamine uptake, and the effects of the drug on this system have been studied to a greater extent than have its noradrenergic or serotonergic effects. Because of this strong relationship between binding to the dopamine transporter (DAT) and the behavioral effects of cocaine, the DAT has on occasion been referred to as the cocaine binding site.

Cocaine also interacts with the vesicular monoamine transporter 2 (VMAT-2) Fig. (**4**), favoring the storage of catecholamines inside synaptic vesicles [48, 49]. It was suggested that Cocaine-induced inhibition of the DAT and increased vesicular sequestration of dopamine, causes a shift in the ratio of cytoplasmic to vesicular dopamine, increasing the amount of neurotransmitter packaged in each vesicle before its release. This effect on the VMAT-2 would contribute to a further increase in synaptic dopamine, upon a depolarizing stimulus [48]. Interestingly, Cocaine metabolite cocaethylene is a more selective indirect dopamine agonist than Cocaine, with relatively weak potency at the serotonin transporter [50].

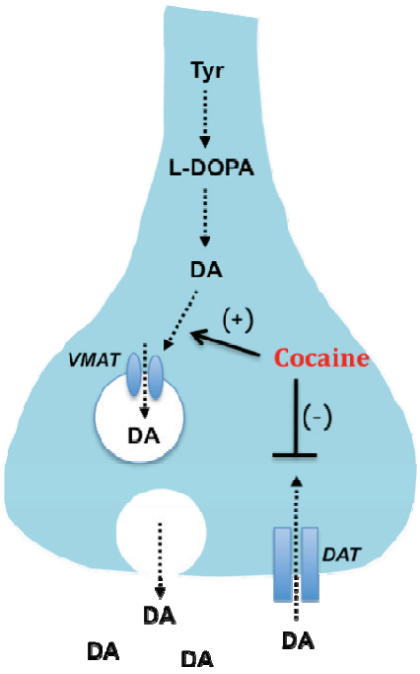

Fig. (4). Cocaine exerts its behavioral effects by enhancing dopaminergic neurotransmission. The mechanism for this effect is inhibition of the dopamine transporter, which blocks dopamine uptake and prolongs the duration of dopamine in the extracellular space. Cocaine can also augment dopamine release by mobilizing a reserve pool of dopamine-containing synaptic vesicles. Tyr: Tyrosine; L-DOPA: L-Dihydroxyphenylalanina; DA: dopamine; VMAT: vescicular monoamine transporter; DAT: dopamine transporter.

Cocaine produces a dose-dependent increase of heart rate and blood pressure accompanied by increased arousal, improved performance on tasks of vigilance and alertness, and a sense of self-confidence and well-being. Higher doses produce euphoria, which has a brief duration and is often followed by a desire for more drug. Involuntary motor activity, stereotyped behaviour, and paranoia may occur after repeated doses. Irritability, increased risk of violence and hallucinations are found among heavy chronic users. Repetitive use of Cocaine results in the depletion of the dopamine stores. This can result both in an intense craving for Cocaine and in what is referred to as a "washed-out" syndrome [51]. Patients experiencing "washed-out" syndrome experience lethargy and anhedonia and have difficulty with muscle movement [52].

The main brain circuits and structures implicated in the effects of the drugs are the ones that mediate reward (nucleus accumbens and ventral pallidum), memory and learning (amygdala and hippocampus), motivation/drive (orbitofrontal cortex and subcallosal cortex) and control (prefrontal cortex and anterior cingulate gyrus) [53]. In drug-addicted individuals, a loss of inhibitory control from the prefrontal cortex impairs the regulation of the activity of the other circuits, perpetuating the cycle of addiction. The latter is the most common complication of Cocaine use. Some users, especially intranasal users can continue intermittent use for years. Others become compulsive users despite elaborate methods to maintain control.

Drug Cocaine Abuse in Developed Countries

The number of cocaine users worldwide ranged from 14 million to 21 million (0·3–0·5% of the population aged 15–64 years). The largest market was North America, then western and central Europe and South America. The global number of opioid users was estimated at 12–21 million people. More than half these users lived in Asia, and the highest levels of use were along the main drug trafficking routes out of Afghanistan [54].

Europe

Cocaine and heroin remain the drugs most strongly associated with drug problems, such as infectious diseases and drug--related death, and the available data do not suggest a decline in the prevalence of their use in Europe. The use of multiple drugs simultaneously or consecutively (polydrug use) is also of concern as it increases risks and complicates drug treatments. These results are presented in the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) Annual report 2009 [25]. The report notes that the use of cocaine is steadily increasing with recent data from general population surveys in different countries pointing to either a stable or rising trend in use in the 15--34 age group. Indirect indicators also point to heroin use no longer declining or being on the increase. In the period 1990 -- 2006 between 6,400 and 8,500 deaths caused by drugs were reported every year, most of which were related to the injection of opioids, and after declining for many years they showed an increase more recently [55].

Between 2006 and 2007, eight countries reported that heroin users entering treatment increased both in number and as a percentage of all treated drug users. In Europe, according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), cocaine is a growing public health issue being the second most commonly used illicit substance among the general European population after cannabis. The estimated number of cocaine consumers is about 12 million Europeans with an overall prevalence of 3.7% of the total adult population (15 – 64 years). Ever in lifetime experience of cocaine is reported by more than 5% of the total adult European population in three countries: UK (7.7%), Spain (7.0%), and Italy (6.6%). The prevalence of use of cocaine is higher among young adults (15 – 34 years), with around 7.5 million young Europeans (5.4% on average) estimated as having used it at least once in their lifetime. In the year 2007, an estimated 3.5 million (2.4%) Europeans young adults have used cocaine, with the highest prevalence levels, of over 3%, being found in Spain, Italy, and the UK [56].

Cocaine is the second most widely trafficked drug in the world, trailing only cannabis in this regard.

Estimates of the prevalence rate for the 27 EU and 4 EFTA countries suggest that the number of cocaine users doubled over the 1998-2006 period. Between 2006 and 2009 consumption appears to have stabilized.

Despite the increase over the last decade in Europe and the decline in North America, overall cocaine use levels in the EU/EFTA region (annual prevalence of 1.2%) are still only half as high as in the USA (2.4% of the popu- lation aged 15-64 in 2009).

Two thirds of European cocaine users live in just three countries: the United Kingdom, Spain and Italy. With Germany and France, these countries represent 80% of European cocaine consumption.

Italy

Significant changes in 2009 were noted in cocaine consumption in northern Italy [57]. In particular, consumption trends in Milan, which were stable from 2005 to 2008 for cocaine and heroin, progressively dropping for THC and increasing for methamphetamine, changed abruptly in 2009, with significant drops in cocaine and heroin consumption, partially compensated by increases in THC and methamphetamine use. The price of this substance in Italy might be comparable and therefore relatively low. Therefore, as costs of street cocaine and heroin in Italy are reported to be higher than for methamphetamine and cannabis this change in consumers. In this scenario of global recession and money worries, illicit drugs consumption might well be considered a luxury that many consumers cannot afford any longer, particularly the expensive illicit drugs such as cocaine and heroin. A recent population survey in Italy showed decreases ranging from 19.4 and 45.7% and 35.9 and 70.3% in respectively lifetime and annual prevalence of illicit drugs users among the general population from 2008 to 2009 [58].

Combined results from the two approaches therefore suggest a real drop in the number of consumers and a shift toward cheaper substances between 2008 and 2009. In spite of conspicuous legislative and social communication efforts in the field by various governments in the last 10 years, the prevalence of drug use was remarkably stable for the most commonly used drugs such as cannabis and cocaine, with a decrease in heroin overbalanced by a marked rise in hallucinogen and stimulant use. Data shows a change in trend between 2005 and 2008; in 2006 the trend for cannabis use and availability dropped and its price rose, while from 2005 cocaine and stimulant use prevalence showed a substantial increase and the price went down. After 2008 the use of all substances seems to have decreased [59].

Over the years, in Italy there has been a strong and substantial decrease in illegal drug prices at street level. Cocaine cost dropped from around J 90/g to about 59 J/g, white heroin from 78.5 J/g to about 53 J/g, MDMA from about 22 J/tablet to about 15 J/tablet. The price of marijuana and hashish remained stable during the observation period, just below 9 J/g for both. Although large regional variations in true price can occur, there is little doubt that these economic indicators should be taken into account when considering trends in use.

However, according to data from the Ministry of the Interior, the purity of seized cocaine and heroin in Italy did not change substantially between 2008 and 2009. Mean cocaine purity was 47% in 2008 and 46% in 2009, and mean heroin purity was 21% in samples seized in 2008 and 2009 [58].

France

Cocaine was the second most frequently tried illegal narcotic after cannabis. Prevalence of use at some point over lifetime has been estimated at about 3% of the French population [60]. Previously associated with closed social groups, cocaine has gradually spread to more diverse environments; fears were expressed of more widespread use a few years ago [61]. Use of cocaine is generally preceded by early use of alcohol, cigarettes and cannabis. Seamen are no exception to this rule: those who had tried cocaine had all used cannabis and more than half reported doing so during the previous month [62].

UK

In the UK the average cocaine purity in police seizures fell from 32% in 2007 to 23% in the first quarter of 2009 [63]. One useful source of data is the British Crime Survey, in which a representative sample of householders was asked about their self-reported use of various illicit substances. According to this, males and individuals in younger age groups reported the highest levels of drug misuse. In people aged 16–24 years, rates of drug misuse have in general fallen. Between 1998 and 2005/2006, use of any illicit drug in the past year declined, with decreases in cannabis and LSD use but increases in the use of cocaine

Ireland

Various sources of evidence suggest that use of cocaine has become more widespread in Ireland in recent years. Official reports

show that, under the misuse of drugs act, offences related to cocaine increased from 11 cases in 1990 to 297 in 2001, and over 1200 in 2005. The number of seizures of cocaine increased from 157 in 1997 to 968 in 2005 [64]. A recent analysis of banknotes in Ireland demonstrated detectable levels of the drug on 100% of euro notes examined.

A marked increase in ICU admissions for the management of cocaine poisoning over the period 2003–2007 has been recorded in Ireland. This is consistent with other measures of cocaine use in Ireland. The patients were typically male and young, and required relatively long ICU stays [65].

Netherlands

In the Netherlands (16.7 million inhabitants), annual cocaine-related addiction treatment demand increased from 8,490 patients in 1994 to 17,270 in 2008, and approximately half of this treatment demand in 2008 concerned users of crack. Although the number of treatment seeking cocaine users slightly decreased in more recent years, the number of cocaine dependent patients that repeatedly returned to addiction treatment increased. Despite its status as one of the most pro- blematic addictions, reliable prevalence estimates of cocaine dependence in the Netherlands are lacking. In 2005, 32,000 current cocaine users were identified in the Netherlands, but this is likely to be a serious under- estimation given the fact that the data were obtained in a population survey [66].

United States

North America is still the subregion with the largest number of cocaine users worldwide (5.7 million in 2009), accounting for more than a third of all cocaine users worldwide. Household surveys in the countries of North America reveal a prevalence rate of annual cocaine use affecting 1.9% of the population aged 15-64 in 2009, down from 2.4% in 2006. The United States of America has the highest prevalence of cocaine use in the region (2.4% of the population, or 5 million people aged 15-64), but there are indications of cocaine use declining over the past few years. Since 2006, among the population aged 12 years and older, there has been a continuing decline in the annual prevalence of cocaine use (from 2.5% in 2006 to 1.9% in 2009), though crack use shows a less rapidly declining trend. The reduction coincided with a supply squeeze in the US cocaine market as less cocaine arrived via Mexico. Purity-adjusted cocaine prices rose by more than 80% between 2006 and 2009.

In addition to significant drops in both annual and past- month cocaine use prevalence, the initiation of new cocaine use also fell. Some 617,000 people aged 12 or older used cocaine for the first time in the past 12 months in the United States in 2009, down from 722,000 a year earlier. Among high school students in grades 8 to 12 in the United States, there has also been a substantial and steady decline in the annual prevalence of cocaine and crack use, especially since 2006. For both cocaine and crack use, the annual prevalence in 2010 among 12th grade students was 2.9% and 1.4%, respectively, which declined from 5.7% and 2.1% respectively in 2006 [67].

Cocaine remains a problem drug in the United States, however. Among the 7.1 million people aged 12 or older who were classified with 'dependence on or abuse of illicit drugs' in 2009, 1.1 million were classified with 'dependence on or abuse of cocaine' [68].

This is nearly one fifth of the annual cocaine users in 2009 – a higher proportion than for all other illicit substances except heroin. In the United States, there were 4.6 million drug-related emergency department visits in the 2009. Among these total visits, the highest rate related to the use of illicit drugs was for cocaine use (137.7 visits per 100,000 inhabitants), followed by cannabis (122.6 per 100,000) and heroin (69.4 per 100,000).

Compared to other illicit drugs, the rate of cocaine-related emergency department visits was much higher among the patients who were 21 years or older (80.9%), indicating continuing problematic use among the older population.

Positive cocaine use hair tests among the general work- force also fell, from 5.3% in 2007 to 2.3% over the first two quarters of 2010. These tests reflect cocaine use over the past three months. Urine tests among the US work- force - reflecting cocaine use over the past two to three days – showed the same, strongly decreasing trend.

Canada

In Canada, the annual prevalence of cocaine use in 2009 was 1.4% among the population aged 15-64, corresponding to some 327,000 people who had used cocaine at least once in the past year. As in the United States, cocaine use has also been decreasing considerably in Canada since 2004, when it was reported as 2.3%. In 2008, it was 1.9% among the 15-64 age group. The past-year prevalence of cocaine use in 2009 was nearly the double (3.0%) among young people (15-24 years old); a rate that has also declined since 2008, when it was reported at 5.9% [69].

CLINICAL IMPLICATION OF COCAINE ABUSE

The effects of Cocaine mainly depend on the user's addiction, the dose received and the mode of assumption. It should be noted that, in the majority of cases, the data on Cocaine addiction derive from case reports and not from randomized clinical trials. Thus, such data are subject to several confounding factors, including type of adulterants and cut, quantity and duration of Cocaine exposure, route of administration, lifestyle and user addiction [54].

Cocaine is a powerful CNS (Central Nervous System) stimulant but exerts its action in a several types of adverse health effects, including acute toxic effects (i.e. overdose, accidental injury and violence), dependence, cardiovascular disease, cirrhosis, blood-borne bacterial and viral infections, and mental disorders (Tab. 1). Of interest, many people who use Cocaine will use also other drugs; therefore, ascribing adverse health effect to a certain drug might be difficult.

1. Cardiovascular Pathology

There is emerging evidence that Cocaine abuse might trigger a variety of cardiac disorders, ranging from arrhythmias to acute myocardial infarction (MI) or even sudden cardiac death. Cocaine affects cardiovascular system in a number of ways, including increasing of systolic and diastolic blood pressure, endothelial dysfunction, hemodynamic alterations, coronary vasoconstriction, hypercoagulability, and direct myocardial and vascular toxicity [70-72]. Furthermore, Cocaine causes the release of norepinephrine and epinephrine from the adrenal medulla, causing significant central and peripheral vasoconstriction [73]. The most important cardiovascular complication in Cocaine addicts is myocardial infarction (MI) [74]. The pathogenesis is multifactorial and complex, basically depending from an increase of myocardial oxygen demand, due to both increasing heart rate and to blood pressure with coronary vasoconstriction, hypercoagulability and accelerating atherosclerosis [75]. While there is a clear increasing in adrenergic activity, there is also an aesthetic effect caused by inhibition of sodium influx across cell membrane during depolarization [76]. Such adrenergic response results in increased intracellular calcium levels and hence in myocardial contractility, which in turn, depends from a direct calcium flux by cocaine-mediated receptor [77]. Mittleman and colleagues showed a 24-fold increased risk of MI in the first 60' after Cocaine assumption in patients who are otherwise at low risk [78]. Overall incidence of cocaine-associated MI is estimated from 0,7 % to 6 % on those presenting chest pain after Cocaine assump-

tion [74, 79]. Focal vasospasm, coronary thrombosis, endothelial dysfunction may be the final cause of MI in non-cardiology patients [78, 79]. Furthermore, early and accelerated atherosclerosis and an increased prevalence of coronary artery aneurysm was described in young cocaine abusers with obstructive coronary artery disease (CAD) [80]. In addition, Cocaine has been found to cause alteration in platelet function and coagulation with a number of cases reported of CAD after its use [81, 82]. Cocaine activates platelets by increasing of platelet factor-4, trhromboglobulin-B and P-selectin [83]; such conditions are associated with an endothelial dysfunction due to increasing production of endothelin-1 with concurrent decrease in nitric oxide production [84]. Moreover, cigarettes smoking, frequently associates with cocaine addiction, causes both endothelial and platelet dysfunction [85], potentiating the Cocaine harmful effects.

Cardiomyopathy, including left ventricle hypertrophy and negative inotropic effect on cardiac muscle, is a well-known but poorly understood effect of Cocaine. Autopsy studies demonstrate that, besides necrosis of the heart, Cocaine may also have a more direct global toxic effect on the myocites in humans. A prominent finding from these studies was myocarditis with mononuclear infiltrate independent from coronary artery disease [86]. The most likely explanation is that excess of catecholamines leads to cell damage by inducing transient vasoconstriction of the coronary vessels which might also leads to foci of necrosis [87]. Moreover, catecholamines may contribute to the production of ROS, which in turn induce myocardial apoptosis [88, 89].

2. Cerebrovascular Pathology

The first report of cocaine-associated stroke was in 1977. Intramuscular administration in a male user was followed 1 h later by aphasia and right sided hemiparesis [90]. Subsequently, the incidence of cerebrovascular accidents increased with the epidemic abuse of Cocaine. Cocaine is associated with both ischaemic and haemorrhagic stroke. As for heart, the causes are unclear but mechanisms seem related both to endothelial dysfunction and alteration in the coagulation system. Of course, ascribing a common pathogenic factor is unlikely, due to the numbers of variables involved. Differently from the heart, Cocaine effect on brain seems independent from a direct toxicity [91]. It has been demonstrated by cerebral angiography that Cocaine induces vasospasm in humans and animals with ischemic stroke [92, 93]. We have previously mentioned the sympathicomimetic effects of Cocaine. Moreover, animal studies suggest that Endothelin-1 is a mediator of cocaine-induced cerebral vasospasm [94]. In conclusion, as to stroke event, Cocaine users show abnormal pattern of cerebral blood flow with reduced glucose metabolism but its relation to associated stroke remains unclear [95, 96]. In addition, cerebral vascular thrombosis as consequence of vasospasm and advanced atherosclerosis has been observed in intracerebral vessels of cocaine-induced cerebral infarction [97]. Although cerebral vasculitis in Cocaine addiction is rarer than other drug-induced stroke (i.e. amphetamines), some reports could be addressed to Cocaine misuse [98]. To this regard, it should be noted that amphetamines may also be present as adulterants in cocaine preparations. Finally, Petty *et al.* reported cardioembolism as the main mechanism of ischemic stroke in Cocaine abuse; cardioembolism, starting from cardiac thrombosis, cold be secondary to cocaine-related cardiomyopathy [99], or due to endocarditis [100].

Cocaine is also associated to haemorrhagic stroke. The mechanism is unclear but it seems related to cocaine-related changes in haemodynamic system. By blocking the catecholamines reuptake, Cocaine induces transient tachycardia and blood pressure elevation [101]. At cerebral level, Cocaine may perturb blood pressure autoregulation, predisposing to vascular breakdown [102].

3. Respiratory Pathology

Exposure of the lung to alkaoidal cocaine (crack-cocaine / free base) and its co-products may lead to severe injury of the airway and lung. Smoking of crack-cocaine can lead to thermal epiglottitis and laryngitis, which may be severe [103, 104]. However, due to the Valsalva manoeuvre performed by the user to accentuate absorption and effects, haemoptysis, haemothorax, pneumothorax and pneumomediastinum (barotrauma) are the main urgent complications following crack-cocaine inhalation. Among sub-acute complication, the most frequent is the so-called "crack-lung". This condition is characterized by acute pulmonary infiltrates associated with a broad spectrum of clinical and histologic findings, such as chest pain, dyspnoea, hypoxemia, interstitial pneumonitis with persistent alveolar infiltrates and bronchiolitis obliterans with organising pneumonia (BOOP) [105]. The clinical presentation of an acute "crack lung", in recognized crack-cocaine addicted, is often acute dyspnoea and hypoxemia with fever, haemoptysis and respiratory failure. Data regarding pathogenesis of the lung in Cocaine abusers are largely incomplete. Cocaine smoking causes bronchostenosis, due to a local irritant effect and not to a pharmacologic effect itself [106]. In autopsy studies, related to Cocaine assumption mainly by intravenous injection or nasal insufflation, the most important finding was medial hypertrophy of small and medium-size pulmonary arteries in 20 % of study population [107], supporting the concept that Cocaine injures the pulmonary microcirculation. It is conceivable that cocaine-smokers develop pulmonary hypertension, however intravenous cocaine administration failed to demonstrate an acute short-term elevation in mean pulmonary arterial pressure assessed by Doppler echocardiography [108].

4. Other Complications

As widely discussed, Cocaine has potent vasoconstictive effects on vascular smooth muscle. As documented in autopsy studies, acute intoxication can cause renal failure and renal infarction by atherogenic damage [109]. Really, the best-known acute renal complication in Cocaine abusers is the acute tubular necrosis related to rabdomyolysis. Cocaine use results in hallucination, agitation and hypertermia. Various drugs abuse may induce brain hyperthermia. While each individual drug (i.e., heroin, cocaine, methamphetamine, MDMA) has its own, dose-dependent effects on brain and body temperatures, these effects are strongly modulated by the individual's activity state and environmental conditions. The effects of hypertermia on skeletal muscle is to reduce calcium requirement for contraction, hence establishing a vicious cycle of heat production secondary to muscle contraction. Such condition results in muscle breakdown with massive release of creatine phosphokinase and myoglobin with acute renal failure [110].

As to vasoactive effects, it should be reported that both inhaled and injected Cocaine might induce mesenteric ischemia, which may lead to perforation [111, 112]. Thus, intestinal α-adrenergic receptors, stimulated by nor-epinephrine, lead to focal ischemia under Cocaine intoxication [101]. Cocaine abuse also causes thrombosis and platelet aggregation which can further explain the incidence of intestinal ischemia.

The same pathophysiological concepts might be transposed to infants born to mothers who abuse Cocaine. They typically have a low birth weight, due to shortened gestation, an incresead risk of sudden infant death syndrome (SIDS), necrotizing enterocolitis, cerebrovascular accidents, congenital abnormalities and behavioural disorders [113].

Death

Global mortality attributable to illicit opioid use was estimated at 100 000 deaths in 1990, 62% of which were in high-income countries. An estimate for 2000 (which defined illicit drug use as

injecting or problem use of amphetamines, cocaine, or opioids) estimated all-cause mortality, and mortality attributable to AIDS, overdose, suicide, and trauma from cohort studies of problem illicit drug users [114, 115].

WHO estimates of global DALYs attributable to amphetamine, cocaine, or opioid use in 2004 suggested that use of these drugs accounted for 0·9% of global DALYs, varying widely across regions. In a recent survey conducted by the US Department of Health and Human Services, only 50% of young people expressed the belief that monthly cocaine ingestion carries a great risk of harm (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [68].

Lucena and colleagues have now provided data to dispel the belief that cocaine use is safe by reporting that 3% of sudden deaths in south- western Spain during their period of observation were cocaine related [56].

In the USA, the lifetime prevalence of recreational cocaine use is currently estimated to be 14%. As its use has increased, the number of cocaine-related cardiovascular events, including angina pectoris, myocardial infarction, cardiomyopathy, and sudden death, has increased commensurately. As a result, it is not surprising that cardiac disease was the most frequent cause of cocaine-related sudden death.

Although cerebrovascular, respiratory and metabolic causes can be involved, cocaine-related sudden deaths are mainly due to cardiovascular complications.

Infact, cardiac hypertrophy, obstructive small vessel disease, and severe premature coronary artery atherosclerosis, with or without thrombosis, are frequent findings, which may account for myocardial ischaemia and cardiac arrest associated with the use of cocaine.

Studies on cocaine-associated deaths, report a male predominance, an average age in the mid-thirties, employed users, death at home and mainly on weekends and are in contrast with heroin-related deaths, where there is no weekend peak, reflecting the high proportions of unemployed users in this population.

Cocaine has been linked to a high incidence of cardiac arrhythmias and sudden death (SD) due to cardiovascular or cerebrovascular complications related to its sympathomimetic effects that result in an increase of heart rate, myocardial oxygen demand, temperature, and blood pressure.

From a pathological viewpoint, acute and chronic abuse of cocaine has been associated with coronary and myocardium abnormalities. The latter include myocardial infarction, myocarditis, cardiac hypertrophy, and dilated cardiomyopathy.

Cocaine use has been also associated with intravascular thrombosis due to platelets aggregation and release of thrombogenic substances from the endothelium.

Anyway, rates of self-reported suicide attempts in problem opioid, cocaine, and amphetamine users are much higher than they are in non-drug-using peers of the same age, sex, and socioeconomic status. The association is probably mediated by depression, rates of which are high in problem drug users. The intoxicating effects of these drugs, and the stresses of an illicit-drug-dependent lifestyle, probably increase suicide risk in depressed drug users. Meta-analyses have produced a pooled crude mortality rate for suicide in opioid-dependent individuals of 0·12 per 100 person-years (95% CI 0·08–0·16) [116-118].

Although cocaine-induced strokes may be less common than seizures, their prevalence has increased in the US since the early 1980s as cocaine use has become more prevalent [93]. A study assessing the risk of stroke associated with cocaine use found a 14-fold increase in risk among cocaine users compared to matched controls [119].

The above complications are potentially fatal and can occur among young, healthy users without any previous risk factors [120]. Moreover, there is no specific combination of conditions under which such outcomes can be predicted. They can occur with small amounts of cocaine and on the first occasion of use [121]. While higher doses and a greater frequency of use increase the likelihood of adverse reactions to cocaine, the thresholds over which complications occur can vary widely between individuals. Thus, while toxic reactions to cocaine are usually dose-related, they are not dose-specific [122].

Due to its powerful reinforcing effects, cocaine is regarded as having a high dependence liability. Cocaine dependence can develop after a relatively short history of use and can be associated with a range of use patterns [123]. Problematic use may be chronic, such that cocaine is used on a daily, or almost daily, basis, or it may be episodic, where the pattern may be to binge on cocaine over a period of hours or days and then abstain for several days. An early indicator of cocaine dependence is when the user finds it increasingly difficult to resist using cocaine if it is available. Smoking and injecting cocaine is associated with a greater dependence liability than intranasal use, with use often progressing to dependence in a matter of weeks or months [124-126]. The onset of dependence as a consequence of intranasal use is much more gradual, typically taking months or even years.

While much is now known about the underlying mechanisms of cocaine dependence, there are still no pharmacological treatments that have been deemed effective in promoting abstinence from cocaine use [127]. Previous research has suggested that a combination of psychotherapy and pharmacotherapy may be more effective in the treatment of cocaine dependence than either approach on its own [128].

Deaths due to cocaine toxicity typically occur among male, experienced drug users who are, on average, in their mid-30s. Cocaine-related fatalities often involve multiple drugs, most commonly heroin and alcohol. Deaths due to cocaine toxicity are due primarily to cardiovascular complications, such as myocardial ischaemia and infarction and cardiac arrhythmias [109, 129-131].

Legal Aspects

It has been estimated that the illegal market for drugs is worth between US$ 100 billion and US$ 500 billion world-wide. These figures are of course no more than estimates, but even at the lower end represents a substantial and lucrative market. Global trends in drug production, transportation and consumption are difficult to describe and assess because of the complexities of the issues involved and the lack of accurate information on what are clandestine activities.

The UN estimates that, in 2007, the European share of the global cocaine seizures (in volume) declined to 11 %, its lowest level since 2004 [132]. In 2007, the total quantity of cocaine seized in Europe dropped to 77 tonnes (120 tonnes in 2006).

Cocaine is transported from South America to the European Union across the Atlantic Ocean by air or maritime routes. Multi-tonne maritime shipments are made from Argentina, Brazil, Chile, Colombia, Ecuador, Suriname and Venezuela to the coastal areas of Spain and Portugal. At the same time, cocaine is also shipped to the major container ports of Belgium, Germany, France, Italy, the Netherlands and the United Kingdom (Project Cola). Although maritime shipments pose the greatest problem because large quantities can be transported at any one time, and detection is difficult, use of individual couriers and of air freight also play an important role.

Three main sea routes to Europe have been identified: the Northern route, leading from the Caribbean via the Azores to Portugal and Spain; the Central route from South America via Cape

Verde or Madeira and the Canary Islands to Europe; and, more recently, the African route from South America to West Africa and from there mainly to Spain and Portugal

Cocaine importation and distribution in Europe is mainly concentrated in western European countries. The Iberian Peninsula is considered the main entry point for cocaine into Europe. In 2007 the Spanish authorities seized almost 38 tonnes of cocaine, much of it at sea, representing about 50 % of the estimated total quantity intercepted in Europe. In Portugal, the amount of cocaine seized has increased rapidly since 2005, with a peak in 2006 at 34 tonnes accounting for 28 % of the European total, whereas in 2007 a total of 7.3 tonnes were seized. This development in Portugal since 2005 points to the use of the Iberian Peninsula by cocaine traffickers as a gateway to the European market. It may also point to a diversification in the unloading points throughout the Iberian Peninsula, in response to the likely intensification in the controls of the traditional cocaine maritime route to the Spanish north-western coast in Galicia. Cocaine also enters Europe via other countries, in particular Belgium, France, Italy, the Netherlands and the United Kingdom, each of which seizes several tonnes of cocaine every year. Other countries are also used to import cocaine into Europe, as flights from the main trafficking routes are increasingly subjected to enhanced controls.

In the US, cocaine is Schedule II according to the provisions of the Controlled Substances Act of 1970. It shares this classification with methamphetamine, morphine and methadone. Schedule II substances have a high potential for abuse but may be administered by a physician for certain purposes. Believe it or not, cannabis is rated in the higher Schedule I category in the U.S [133].

Possession of more than 500 grams of cocaine are as follows:

- Imprisonment for five to 40 years.
- Where a death or serious injury can be traced to the cocaine, the penalties increase to a prison sentence of 20 years to life and/or a fine of up to $2 million for an individual defendant and up to $5 million where the defendant is not an individual.
- When the conviction is handed down where the defendant has a prior conviction for a felony drug offense that has not been completed, he or she will be sent to prison for 10 years to life.
- If death or serious injury resulted from the cocaine use and the defendant has a prior conviction, he or she will be sent to prison for life and/or be required to pay a fine of up to $4 million for an individual and up to $10 million if the defendant is other than an individual. Penalties for possession of more than 5 kg of cocaine or a substance containing coca leaves are severe.
- Minimum of 10 years to life in prison and/or a fine of up to $4 million for an individual defendant; fine of up to $10 million if the defendant is not an individual.
- In a case where death or serious bodily injury resulted from the drug use, the prison sentence doubles to 20 years to life.
- If the accused is convicted before the penalty for a previous felony drug offense has been completely finished, he or she may be sentenced to prison for 20 years to life.
- In the case of a subsequent drug offense where death or serious injury resulted from the drugs, a fine of up to $8 million for an individual defendant and up to $20 million where the defendant is not an individual may also be imposed.

Along with the criminal penalties listed above, an individual who is found in possession of a small amount of cocaine may be subject to civil penalties. A fine of up to $10,000 per violation may be imposed. In deciding the level of the fine, the court may consider the individual's income and assets.

In the UK, cocaine is a Class A substance under the Misuse of Drugs Act 1971. Other Class A substances include ecstasy, heroin, LSD and crystal meth. Drugs in this class are strictly controlled and are not authorized for any medical purpose. They cannot be possessed, supplied or used for any purpose unless a special Home Office License has been obtained, and these are usually issued allowing the substance to be used for research.

- The penalties for possession of cocaine are an unlimited fine and up to seven years in jail.
- A conviction for trafficking or producing coke carries an unlimited fine and/or life in prison.

The way that police forces in the UK deal with drug offenders varies by region. In some cases, a person caught with a small amount of the drug will be cautioned and not arrested. Often incarceration for use can be avoided by checking-in to a court approved cocaine rehab program. When a drug case does get to court, some jurisdictions are more likely to impose a substantial fine or send the offender to prison than others.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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